REMARKS

Initially, the Examiner acknowledges Applicants' claim for foreign priority and indicates that the certified copy of the priority document has been received. However, there is no claim to foreign priority and no certified copy of the priority document has been submitted.

In the present Amendment, the claims have been amended to delete the recitation of "or R^b and R^c, together with the N atom to which they are attached, form a group ... (vi) $NRgR^{b}$" from the definition of "(3) $-NR^bR^c$" in the definition of R^3. The claims have also been amended to delete the recitations of "(vi) heteroaryl, unsubstituted or substituted with one or more hydroxy, C_{1-10} alkoxy, C_{1-10} alkyl or halogen" from the definition of "R^a" in the definition of R^3 and "(v) heteroaryl, unsubstituted or substituted with one or more hydroxy, C_{1-10} alkoxy, C_{1-10} alkyl or halogen, and" from the definition of "R^b, R^c, R^e and R^f" in the definition of R^3. The claims have also been amended to delete the recitation of "hydrogen" from the definition of R^5 and R^6. In addition, the claims have been amended to recite "~~and~~ or (pharmaceutically acceptable) salts thereof." Claims 33-36 have been cancelled without prejudice or disclaimer. No new matter has been added, and entry of the Amendment is respectfully requested.

Upon entry of the Amendment, claims 1-32 will be pending.

At page 2 of the Action, claims 1-36 are rejected under 35 U.S.C. § 112, first paragraph, because, per the Examiner, the specification, while being enabling for one N-containing 5 and 6 membered ring compounds, does not reasonably provide enablement for the broader scope in claims 1, 27 and claims dependent thereon.

Further, the Examiner states that the scope of mono or poly-ring 3- to 8-membered heteroaryl having 1 to 3 heteroatoms is not adequately enabled.

As noted, the term "heteroaryl" and related recitations have been deleted from the claims. Accordingly, withdrawal of the § 112 rejection is requested.

At page 5 of the Action, claims 34-36 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Claims 34-36 have been cancelled, rendering this rejection moot.

At page 7 of the Action , claims 1-33 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nakazato et al (US 6,333,428) and/or Massey et al (US 6,160,009).

Applicants submit that this rejection should be withdrawn because Nakazato et al and Massey et al do not disclose or render obvious the present invention, either alone or in combination.

Applicants submit herewith a copy of J. Org. Chem., 2005, 70, pages 8027-8034, as a reference written by the inventors. This reference was published after the filing of the present application and advantageous effects of the present invention are clearly disclosed therein.

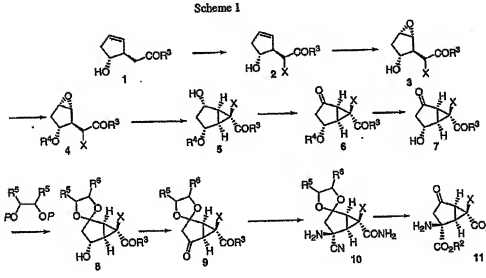
As disclosed in the "Background of the Invention" in the present specification, the process described in Nakazato et al requires the step of preparing a racemic intermediate and thus needs complicated separation steps, which leads to the deterioration of productivity (page 1, last line to page 2, line 15 of the specification; and col. 8, line 57 and col. 9, line 6 of Nakazato et al).

By the process described in Massey et al, an aminonitrile is obtained as a synthetic compound, which corresponds to an unprotected form of a compound of formula (IX) of the present application. The aminonitrile obtained in Massey et al is a mixture of diastereomer compounds. Thus, to obtain a desired diastereomer compound, a separation process is needed (col. 10, line 66 to col. 11, line 6 of Massey et al).

In contrast, by the process of the present invention, the final product can highly selectively be obtained without racemic resolution of intermediates. Specifically, the following effects can be obtained.

First, in the stereoselective synthesis from the Compound 1 to the Compound 5 shown in Scheme 1 at page 17 of the specification (shown below), the enantiomerically pure intermediate compound of the formula (II), corresponding to the Compound 5 in Scheme 1, is used.

Scheme 1



Second, in the process of Nakazato et al, a toxic compound, $(PhSe)_2$(diphenyldiselenide), is used (col. 7, line 56 to col. 8, line 3). In contrast, according to the presently claimed process, the compound of the formula (II) can be obtained without using such a hazardous material.

Finally, advantageous effects disclosed in the reference, J. Org. Chem., 2005, 70, pages 8027-8034, can be achieved, specifically as follows.

Regarding the difficulty of selecting a protecting group of the ketone compound of the formula (V) of the present invention, the above reference describes the following (page 8030, left column).

(i) Although the ethylene dithioketal of **17**, corresponding to the presently claimed compound of formula (V), was readily prepared and performed well in the Strecker reaction, the final hydrolysis was difficult under a variety of conditions, resulting in the formation of a complex mixture.

(ii) Protection of ketone 17 as a simple ketal (methanol, ethanol, and 2-propanol) gave ethers at the beta-position of the ketone, that is, beta-alkoxyketone was formed.

(iii) Cyclicketal from ethylene glycol was not stable to Strecker conditions. Sterically bulky diols, such as pinacol, gave only enone form.

Eventually, by protecting ketone with the presently claimed compound of formula (VI) having methyl(2,3-butanediol) or phenyl(hydrobenzoin) as R^5 and R^6, the present invention is achieved (page 10, lines 9-10 and page 20, lines 9-13 of the specification).

As discussed above, for the compound of formula (V), there is difficulty selecting a protecting group of ketone.

In addition, the following unexpected effects were obtained by the use of ketal-ketone compound of formula (VIII).

First, Strecker reaction yielded the desired amino-nitrile compound of formula (IX) with high diastereoselectivity (page 21, lines 1-6 of the specification). This compound was highly crystalline. The crystalline of the amino-nitrile compound (IX) was able to be isolated as a single isomer by completely leaving unwanted diastereomer in the mother liquid using a simple crystallization process (page 32, Example 9 of the specification; and J. Org. Chem. 70, 2005, page 8030, right column).

Second, in Nakazato et al, hydrolysis under severe condition where H_2SO_4 is used at high temperature (145 degrees centigrade) for five days is required at the final step of the synthesis,

causing a low yield and difficulty in the isolation of the final product (page 3, lines 11-14 of the specification; and column 21, Example 13 of Nakazato et al).

In contrast, the presently claimed synthetic method enables the "global hydrolysis" of amino-nitrile compound at three positions at the same time under much more moderate condition by using acetic acid and hydrochloric acid at lower temperature (75 degrees centigrade) for 4 to 5 hours (page 21, lines 7-12; and pages 32-33, Example 10 of the specification). Other possible conditions include, for example, that in the presence of H_2SO_4 at around 100 degrees centigrade for 2 hours, and that in the presence of acetic acid/ H_2SO_4 at around 60 degrees centigrade for 2 hours.

In addition, a benzylphenyl ketone generated in this hydrolysis as a by-product derived from hydrobenzoin was easily removed by simple extraction procedure with CH_2C1_2 by which the crystalline hydrochloride salt of the compound of formula (IA) was able to be obtained in high yield and high purity (pages 32-33, Example 10 of the specification; and J. Org. Chem. 70, 2005, page 8030, right column).

As discussed above, the presently claimed process makes it possible to synthesize the enantiomerically pure intermediate compound, to avoid using a toxic reagent, to obtain the desired final product with high selectivity, and to remove an unwanted diastereomer or impurities without a column purification by a silica gel or an ion exchange resin.

Accordingly, the present claims are not obvious and are patentable over Nakazato et al and Massey et al, either alone or in combination.

In view of the above, reconsideration and withdrawal of the §103(a) rejection based on Nakazato et al and Massey et al are respectfully requested.

Allowance is respectfully requested. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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JOC*Article*

Stereoselective Syntheses of Highly Functionalized Bicyclo[3.1.0]hexanes: A General Methodology for the Synthesis of Potent and Selective mGluR2/3 Agonists

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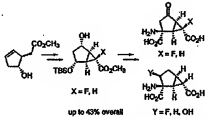

A Et_2Al mediated intramolecular epoxide opening, cyclopropanation reaction is described. The transformation provided highly functionalized bicyclo[3.1.0]hexane systems in high efficiency and with perfect H or F endo selectivity. Application of this reaction to the synthesis of mGluR2/3 agonist **1** (43% overall yield) and a few intermediates suitable for the synthesis of other bicyclo[3.1.0]hexane mGluR2/3 agonists is discussed.

Introduction

L-Glutamate is a major excitatory neurotransmitter in the mammalian central nervous system.[1] Drugs that modulate glutamate activity hold promise for treating an exceptionally wide range of disorders, including schizophrenia, depression, anxiety, addiction, pain, epilepsy, and neurodegenerative diseases such as Parkinson's and Alzheimer's. Currently, glutamate receptors are classified into two broad types: the ionotropic glutamate receptors (iGluRs) and the metabotropic glutamate receptors (mGluRs).[2,3] The latter mGluRs are further classified into eight subtypes and three groups (I−III). The discovery of mGluRs represents one of the most noteworthy advances in glutamate research.[4] The mGluRs activate biochemical processes within cells, and are capable of subtle modulatory actions.

In recent years, highly selective, orally active, and potent Type II/III mGluR (mGluR2/3) agonists have been reported.[5] Some of them possess a densely functionalized bicyclo[3.1.0]hexane skeleton and are shown in Figure 1. These compounds are designed as constrained glutamic acid analogues that closely mimic the proposed bioactive conformation of the neurotransmitter when acting at the specific receptor. They also offer a unique synthetic challenge because they incorporate many functional groups and four or five contiguous chiral centers in a relatively small molecule. Although syntheses of these

(1) Collingridge, G. L.; Lester, R. A. *Pharmacol. Rev.* **1989**, *40*, 143.
(2) Sommer, B.; Seeburg, P. H. *Trends Pharmacol. Sci.* **1992**, *13*, 291.
(3) (a) Nakanishi, S. *Science* **1992**, *258*, 597. (b) Schoepp, D. D.; Conn, P. J. *Trends Pharmacol. Sci.* **1993**, *14*, 13. (c) Nakanishi, S.; Masu, M. *Ann. Rev. Biophys. Biomol. Struct.* **1994**, *23*, 319. (d) Hollmann, M.; Heinemann, S. *Annu. Rev. Neurosci.* **1994**, *17*, 31. (e) Pin, J. P.; Duvoisin, R. *Neuropharmacology* **1995**, *34*, 1. (f) Schoepp, D. D.; Jane, D. E.; Monn, J. A. *Neuropharmacology* **1999**, *38*, 1431. (g) Pin, J. P.; Acher, F. *Curr. Drug Targets* **2002**, *1*, 297.
(4) Holden, C. *Science* **2003**, *300*, 1866.

(5) (a) Monn, J. A.; Valli, M. J.; Massey, S. M.; Wright, R. A.; Salhoff, C. R.; Johnson, B. G.; Howe, T.; Alt, C. A.; Rhodes, G. A.; Robey, R. L.; Griffey, K. R.; Tizzano, J. P.; Kallman, M. J.; Helton, D. A.; Schoepp, D. D. *J. Med. Chem.* **1997**, *40*, 528. (b) Helton, D. R.; Tizzano, J. P.; Monn, J. A.; Schoepp, D. D.; Kallman, M. J. *Neuropharmacology* **1997**, *36*, 1511. (c) Moghaddam, B.; Adams, B. W. *Science* **1998**, *281*, 1349. (d) Monn, J. A.; Valli, M. J.; Massey, S. M.; Hansen, M. M.; Kress, T. J.; Wepsiec, J. P.; Harkness, A. R.; Grutsch, J. L., Jr.; Wright, R. A.; Johnson, B. G.; Andis, S. L.; Kingston, A.; Tomlinson, R.; Lewis, R.; Griffey, K. R.; Tizzano, J. P.; Schoepp, D. D. *J. Med. Chem.* **1999**, *42*, 1027. (e) Nakazato, A.; Kumagai, T.; Sakagami, K.; Yoshikawa, R.; Suzuki, Y.; Chaki, S.; Ito, H.; Taguchi, T.; Nakanishi, S.; Okuyama, S. *J. Med. Chem.* **2000**, *43*, 4982. (f) Pellegrini, C.; Prezzo, W. *Bioorg. Med. Chem.* **2002**, *10*, 433.

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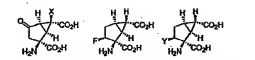
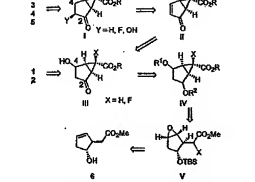


1: X = F (MGS0028) 3: (MGS0008) 4: Y = H (LY354740)
2: X = H (LY418425) 5: Y = OH (Ro 65-3479)

FIGURE 1. Highly selective and potent mGluR2/3 agonists.

SCHEME 1. Synthetic Plan for MGluR2/3 Agonists 1–5



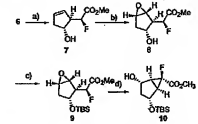
compounds have been reported, most of them were racemic syntheses and required chiral HPLC column separations.[5,8] Herein we report a highly efficient and general approach toward these molecules and a large-scale preparation of **1**, one of the most selective and potent agonists.

Results and Discussion

Synthetic Plan. The synthetic plan called for the initial construction of the selectively protected bicyclic diol **IV** in Scheme 1. Hydroxy ketone **III** resulting from oxidation of **IV** was expected to be suitable for the installation of the amino acid functional groups in **1** and **2**. Compound **III**, through enone **II** or its saturated analogue, was also set for the preparation of **I**, an intermediate designed for the introduction of the amino acid functionality in 3–5. An intramolecular cyclopropanation reaction between the epoxide and the ester enolate of **V**, prepared from the known compound **6**,[7] would provide **IV** with the highly functionalized bicyclo-[3.1.0]hexane skeleton. Thus, this intramolecular cyclopropanation reaction became the cornerstone of our synthesis.

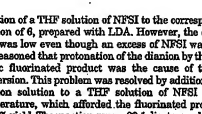
Stereoselective Synthesis of Monoprotected Fluorinated Diol 10 (IV, X = F). The key intermediate, monoprotected fluorinated diol **10**, was synthesized as depicted in Scheme 2. Fluorination of chiral methyl ester **6** was accomplished with *N*-fluorobenzenesulfonimide (NFSI, **13**).[8] Initially, the reaction was carried out by

SCHEME 2. Stereoselective Preparation of 10 (IV: X = F)[a]



[a] Reagents and conditions: (a) (i) LDA, THF, −70 °C, (ii) NFSI (13), −82 °C, 84%; (b) TBHP, VO(acac)$_2$ (2–4 mol %), toluene, 0–40 °C, 91%; (c) TBSCl, imidazole, DMF, 0–25 °C, 95%; (d) Et$_2$Al, LiHMDS, −60 °C, 56%.

SCHEME 3. Diastereoselective Fluorination of 6



addition of a THF solution of NFSI to the corresponding dianion of **6**, prepared with LDA. However, the conversion was low even though an excess of NFSI was used. We reasoned that protonation of the dianion by the more acidic fluorinated product was the cause of the low conversion. This problem was resolved by addition of the dianion solution to a THF solution of NFSI at low temperature, which afforded the fluorinated product **7** in 84% yield. The reaction gave ~2:1 diastereoselectivity at the α carbon of the fluoroester. The absolute configuration of the newly generated chiral center is not clear, but the *S*-configuration is consistent with the proposed chelated structure of the dianion **11** (Scheme 3), where fluorinating reagent **13** approaches from the less hindered side. The major impurity of the reaction was the corresponding *O*-benzenesulfinate **12**, which was suppressed at low temperatures (<−78 °C).

A trans relationship between the methyl fluoroacetate group and the epoxide is required for cyclopropanation. To take advantage of the free hydroxyl group, which is trans to the methyl fluoroacetate group, vanadium-mediated epoxidation of homo-allylic alcohol was applied.[9] Epoxide **8** was isolated in 91% yield as the sole diastereomer. The desired trans relationship in **8** was supported by nOe analysis (Figure 2). The hydroxyl group was protected with a TBS group, leading to crystalline TBS ether **9** in 95% yield.

With the requisite trans epoxide **9** in hand, we then addressed the key intramolecular epoxide opening to construct the functionalized bicyclo[3.1.0]hexane skeleton.[10] No desired bicyclic compound **10** was observed when **9** was treated with excess LiHMDS at −78 °C, followed by warming to 0 °C and aging for 5 h.[11] After aqueous workup, a portion of the starting material was

(6) (a) Domínguez, C.; Ezquerra, J.; Prieto, L.; Espada, M.; Pedregal, C. *Tetrahedron: Asymmetry* **1997**, *8*, 511. (b) Ohfune, Y.; Demura, T.; Iwama, S.; Matsuda, H.; Nanbu, K.; Shimamoto, K.; Shinada, T. *Tetrahedron Lett.* **2003**, *44*, 5431.

(7) (a) Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 7171. (b) Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *Org. Synth.* **1988**, *53*, 44.

(8) Differding, R.; Ofner, H. *Synlett* **1991**, *3*, 187.

(9) For directed epoxidation, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

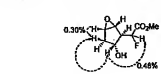


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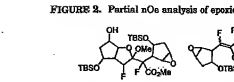
FIGURE 2. Partial nOe analysis of epoxide 8.



14 15

FIGURE 3. Major byproducts from lithium enolate of 9.

recovered together with unidentified impurities. Based on its ^1H NMR, the recovered epoxide was the epimer at the α-position of the fluorester. The result suggested that the enolate of **9** was indeed generated and that activation of the epoxide may be required for this cyclization. Lewis acids were examined,[10] and we found that addition at −78 °C of a stoichiometric amount of Et_2AlCl to a THF solution of the anion, generated from the reaction of **9** with LDA or LHMDS, gave product **10** in ~60% yield. With 10 mol % of $Sc(OTf)_3$, the cyclization of the anion (with LHMDS) went slowly, and **10** was obtained in ~60% yield after 37 h at −50 °C. Addition of a stoichiometric amount of $Sc(OTf)_3$ accelerated the reaction, but the outcome was similar to the catalytic reaction. The $BF_3{\cdot}Et_2O$ mediated reaction proceeded rapidly, and though the reaction was complete in 45 min at −78 °C, it afforded **10** in only 30% yield. Inverse addition of the enolate solution to a solution of Lewis acid, such as Et_2AlCl, Et_3Al, $Ti(OiPr)_4$, and $Zn(OTf)_2$, did not improve the results. The major byproducts of these reactions were identified as dimers **14** and **15** by NMR analyses (Figure 3). It was speculated that formation of dimers had come from the Claisen condensation of the enolate as fluoroester enolates are prone to self-condensation.[11] To avoid this problem, epoxide **9** was premixed with Lewis acid prior to enolate generation.

LHMDS was slowly added to a mixture of epoxide **9** and Et_2AlCl at −78 °C. After 4.5 h, product **10** was isolated in 74% yield together with 12% of **9**. Further studies improved the results as summarized in Table 1. The best Lewis acid was Et_3Al, and **10** was isolated in 96% yield when **9** was treated with 1.2 equiv of Et_3Al

(10) (a) An intramolecular cyclopropanation reaction of ester enolate to an iodide has been reported and complete F-endo products were observed. See: Saito, A.; Ito, H.; Taguchi, T. *Tetrahedron* **2001**, *57*, 7457. (b) Yoshikawa, N.; Yan, L.; Yasuda, N.; Yelamos, R. F.; Tilyer, R. D. *Tetrahedron Lett.* **2004**, *45*, 7261. (c) Zhang, F.; Song, Z. J.; Tschaen, D.; Volante, R. P. *Org. Lett.* **2004**, *6* (21), 3775.

(11) Agami, C.; Couty, F.; Evano, G. *Tetrahedron Lett.* **2000**, *41*, 8301.

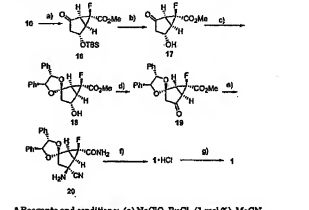
(12) For Lewis acid assisted epoxide opening with enolates, see: (a) Taylor, S. K.; Fried, J. A.; Grassi, V. N.; Marolewski, A. E.; Felton, E. A.; Pool, T.-J.; Rosanka, B. S.; Whitaker, M. R. *J. Org. Chem.* **1993**, *58*, 7304. (b) Crotti, P.; Bussolo, V. D.; Favero, L.; Pineschi, M.; Pasero, M. *J. Org. Chem.* **1996**, *61*, 9548. (c) Crotti, P.; Bussolo, V. D.; Favero, L.; Macchia, F.; Pineschi, M.; Nepoliteano, E. *Tetrahedron* **1999**, *55*, 6853. (d) Hojo, M.; Sakata, K.; Matsuki, K.; Ueno, J.; Nishikori, H.; Hosomi, A. *Chem. Lett.* **2002**, 142.

(13) (a) Brandänge, S.; Dahlman, O.; Morch, L. *J. Am. Chem. Soc.* **1981**, *103*, 4452. (b) Welch, J. R.; Seper, K.; Eswarakrishnan, S.; Samartino, *J. J. Org. Chem.* **1984**, *49*, 4720.

TABLE 1. Epoxide Opening Cyclopropanation of 9

entry	Lewis acid	time (h)	temp (°C)	10 (%)
1	$Al(OiPr)_3$	5	−78	trace
2	$Ti(OiPr)_4$	5	−78	trace
3	$BF_3{\cdot}Et_2O$	4.5	−78 to 0	trace
4	Et_2Zn	4.5	−78 to 0	67
5	Et_2AlCl	4.5	−78	74
6	Et_2Al	6	−78	96
7	Et_2Al	1	−60	96
8	Et_3Al	0.5	−20	70

SCHEME 4. Preparation of Agonist 1 from Monoprotected Diol 10[a]



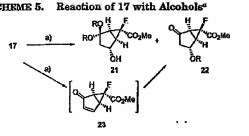
[a] Reagents and conditions: (a) NaClO, $RuCl_3$ (1 mol %), MeCN, 0 °C; (b) 1 M HCl, 25 °C, 95% from **10**; (c) (*S,S*)-PhCH(OTMS)-CH(OTMS)Ph, TfOH (10 mol %), CH_2Cl_2, 0 °C, 100%; (d) NaClO, $RuCl_3$ (0.5 mol %), MeCN, AcOH, 0 °C, 93%; (e) $NH_2OH{\cdot}HCl$, $Ti(OiPr)_4$, TMSCN, −10 to 0 °C, 80%; (f) HCl (3 M), AcOH, 75 °C; (g) H_2O, 94% from **20**.

followed by addition of 1.4 equiv of LHMDS at −60 °C for 1 h. When run at −20 °C, the reaction was not as clean, and the yield of **10** suffered (70%). Lower temperature (−78 °C) increased the reaction time to 6 h in the same yield (96%). The stereochemistry at C-6 was perfectly controlled, and only the F-endo product was obtained, as confirmed by a single-crystal X-ray analysis of subsequent intermediate **19**. Thus, an unprecedented, highly efficient, enantioselective cyclopropanation reaction was realized for the construction of these densely substituted bicyclo[3.1.0]hexane systems. To the best of our knowledge, the reaction described here represents the first example of an epoxide opening with a fluoroester enolate (intramolecularly or intermolecularly). The enolate stability issue was addressed by the precomplexation of epoxy ester **9** and a Lewis acid.

Preparation of Agonist 1 from Monoprotected Diol 10. The conversion of **10** to agonist **1** is summarized in Scheme 4. Monoprotected diol **10** was first converted to hydroxy ketone **17**. Of the many choices for oxidation of **10**, we used a $RuCl_3$-mediated oxidation with bleach.[14] Crystalline TBS ketone **18** was isolable, but instead, the crude solution of **18** was subjected to hydrolysis with 1 M HCl, and hydroxy ketone **17** was isolated as a crystalline compound in 95% overall yield from **10**.

(14) Cai, D.; Hughes, D. L.; Verhoeven, T. R. *Tetrahedron Lett.* **1996**, *37*, 2537.

SCHEME 5. Reaction of 17 with Alcohols[a]



[a] Reagents: (a) alcohol, BF_3OEt_2.

Next, we turned our attention to the installation of the amino acid functionality. Reported methods for this transformation had many drawbacks,[6] including a slow reaction (5 days) for hydantoin synthesis and harsh global hydrolysis conditions (60% H_2SO_4, 145 °C, 6 days). Furthermore, the instability of 1 in aqueous and/or organic solvents made this preparation more challenging, especially because 1 had previously been isolated by resin chromatography.[15] It would be ideal to avoid protection of the ketone and directly install the amino acid moiety onto hydroxy ketone 17 or TBS protected 16. However, complex mixtures were obtained in all the attempted amino acid installation reactions including the Bucherer–Bergs hydantoin formation reaction and the titanium-mediated Strecker reaction.[16,17] Therefore, we protected ketone 17.

Although the ethylene dithioketal of 17 was readily prepared and performed well in the Strecker reaction, the final hydrolysis was difficult under a variety of conditions, resulting in the formation of a complex mixture. Protection of ketone 17 as a simple ketal was deemed ideal for global hydrolysis at a later stage, but formation of acyclic ketals with methanol, ethanol, and 2-propanol all gave ethers at the β-position of the ketone (22, Scheme 5) via enone 23. Although we prepared a cyclic ketal from ethylene glycol, it was not stable to Strecker conditions. Sterically bulky diols, such as pinacol, gave only enones 23. 2,3-Butanediols and hydrobenzoins were considered hindered enough to avoid conjugate addition yet small enough to permit ketalization. The ketals were prepared by reaction of the bis-*O*-TMS ethers of the diols with 17 in the presence of 10 mol % of TfOH in CH_2Cl_2.[18] For example, reaction of the bis-*O*-TMS ether of (*S*,*S*)-hydrobenzoin with 17 gave the hydroxy ketal 18 in quantitative yield. Oxidation of 18 with NaOCl in MeCN in the presence of $RuCl_3$ (0.5 mol %) and AcOH yielded crystalline ketal-ketone 19 in 93% isolated yield. Other ketal-ketones 24–26 were prepared similarly (Figure 4), and all successfully extended into the Strecker reaction.

Strecker reactions of ketal-ketones 19 and 24–26 were evaluated. The diastereoselectivity and yields are summarized in Table 2. Ketal-ketone 19 derived from (*S*,*S*)-hydrobenzoin proved the best based on the diastereoselectivity of the Strecker reaction and the crystallinity of related intermediates. Treatment of 19 with ammonia and titanium isopropoxide in methanol at room temperature, followed by the addition of TMSCN at −10 to 0 °C gave the aminonitrile 20 in a 13.1:1 diastereomeric ratio. The reaction was complete in 20 h, and the highly crystalline compound 20 was isolated as a single isomer in 80–85% yield by filtration of the crude reaction.

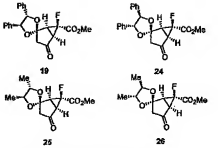


FIGURE 4. Stable ketal ketones evaluated.

TABLE 2. Strecker Reaction of Ketal Ketones

entry	ketal ketone	diastereo ratio[a]	HPLC assay yield [%][b]
1	19	13.1:1	83.2
2	24	6.9:1	71.9
3	25	7.1:1	76.9
4	26	6.3:1	80.4

[a] Ratios were determined by ^{19}F NMR and were designated as the ratio of desired diastereomer to unwanted diastereomer. [b] Yield of major diastereomer.

Global hydrolysis of aminonitrile 20 was accomplished in 5 h using a 1:3 (v/v) mixture of AcOH and 3 M HCl at 75 °C. During the hydrolysis, hydrobenzoin from the ketal moiety was converted into benzyl phenyl ketone, which was removed by extraction with CH_2Cl_2. The aqueous layer was concentrated to yield the crystalline hydrochloride salt of 1, which was converted to 1 by simply dissolving the salt in water and adjusting the pH to 1.55. Agonist 1 was isolated as the monohydrate in 94% yield, and the physical properties and spectroscopic and biological data were all consistent with that reported and an authentic sample.

Application to the Synthesis of Other mGluR Agonists. The successful preparation of 1 encouraged us to investigate the application of our methodology to the synthesis of mGluR2/3 agonists 2–5. As previously discussed, the selectively protected bicyclic diol 28 (TV, X = H in Scheme 1) would serve as a key intermediate for all these compounds. The synthesis of 28 is summarized in Scheme 6. Hydroxyl group directed epoxidation of 6 mediated by $VO(acac)_2$ followed by protection of the hydroxyl group as a TBS ether gave 28 in 65% overall yield. The Lewis acid-mediated cyclopropanation reaction of epoxide 28 provided 29 in 99% yield. The reaction proceeded more rapidly (1.5 h) than the fluorinated analogue 9 at −78 °C, presumably a result of the higher nucleophilicity of the enolate lacking a fluorine atom. Again, the stereochemistry was perfectly controlled based on nOe experiments (Figure 5).

(15) Compound 1 is not stable in DMSO-d_6 at room temperature and was decomposed completely to a mixture of several aromatic compounds in 3–5 days.

(16) In ref 5a, the desired hydantoin was obtained in 16% yield from the ethyl ester of the enantiomer of hydroxy ketone 17 under Bucherer–Bergs conditions.

(17) Festal, D.; Nguyen Van Nhien, A.; Pillon, M.; Vills, F.; Ronco, G. *Tetrahedron Lett.* **2000**, *41*, 6403.

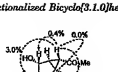
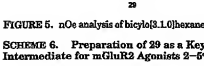


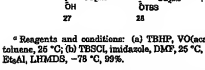
FIGURE 5. nOe analysis of bicylo[3.1.0]hexane derivative 29.

SCHEME 6. Preparation of 29 as a Key Intermediate for mGluR2 Agonists 2–5[a]



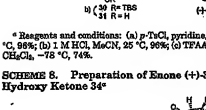
[a] Reagents and conditions: (a) TBHP, VO(acac)$_2$ (4 mol %), toluene, 25 °C; (b) TBSCl, imidazole, DMF, 25 °C, 65% from 6; (c) Et$_3$Al, LHMDS, −78 °C, 99%.

SCHEME 7. Preparation of Enone (−)-32[a]



[a] Reagents and conditions: (a) *p*-TsCl, pyridine, CH_2Cl_2, 0–25 °C, 98%; (b) 1 M HCl, MeCN, 25 °C, 90%; (c) TFAA, DMSO, TEA, CH_2Cl_2, −78 °C, 74%.

SCHEME 8. Preparation of Enone (+)-32 and Hydroxy Ketone 34[a]



[a] Reagents and conditions: (a) TFAA, DMSO, TEA, CH_2Cl_2, −78 °C, 94%; (b) DBU, CH_2Cl_2, 82%; (c) 1 M HCl, CH_3CN, 79%.

Monoprotected diol 29 is a versatile intermediate that permits ready conversion to either enantiomer of enone 32, the ethyl ester of which had been reported as the key intermediate for 2–5.[5,6]

Enone (−)-32 was obtained as shown in Scheme 7. Activation of the hydroxyl group of 29 as the tosylate followed by removal of the TBS group provided free alcohol 31 in high yield. Swern oxidation of 31 using TFAA and DMSO gave the ketone. Simultaneously, elimination of the tosyl group occurred during the reaction to give enone (−)-32 in an unoptimized yield of 74%.

Enone (+)-32 was prepared as shown in Scheme 8. Swern oxidation of 29 provided ketone 33, and elimination of the TBSO group with DBU provided enone (+)-32. Thus, both enantiomers were efficiently accessed. The corresponding ethyl esters of 32 have been used for the preparation of 2–4.[5,6] Furthermore, hydroxy ketone 34, which would be a key intermediate for 2, was prepared by mild acidic hydrolysis of 33.[19] That both enantiomers of 6 are readily accessible from sodium cyclopentadienide makes this method flexible and general.

Conclusion

In summary, we have developed a general and highly efficient asymmetric synthesis of potent and selective bicyclo[3.1.0]hexane mGluR2/3 agonists. Densely functionalized, enantiomerically pure, monoprotected diols 10 and 29 were prepared via a Et$_3$Al-mediated intramolecular cyclopropanation with perfect H or F endo selectivity in excellent yields. This key transformation sets all functional groups within the targeted bicyclo[3.1.0]-hexane systems with high efficiency. The instability of the corresponding fluoro enolate was avoided by precomplexation of the epoxide with Lewis acids, and the conditions were found applicable to the formation of analogue 29, which was converted into both enantiomers of enone 32 efficiently. Both enones are precursors to agonists 2–5. Fluorinated monoprotected diol 10 was converted to 1, one of the most potent and selective agonists. Ketal protection with (*S,S*)-hydrobenzoin, followed by a titanium-mediated Strecker reaction served as a mild method for the introduction of the amino acid moiety in high stereoselectivity and efficiency. A mild global hydrolysis was developed, addressing the previously troublesome ketone protecting group strategy. The overall yield of 1 by this route from enantiomerically pure hydroxy methyl ester 6 was 43% in 10 steps, and this highly robust synthesis of 1 was applicable to other bicyclo[3.1.0]hexane mGluR2/3 agonists.

Experimental Section

Methyl (2*S*)-Fluoro[(1*R*,5*R*)-5-hydroxycyclopent-2-en-1-yl]acetate (7). To a solution of diisopropylamine (10.8 mL, 76.8 mmol) in THF (28 mL) was added a solution of butyllithium (28.2 mL, 70.4 mmol, 2.5 M in hexanes) over 40 min while the inside temperature was maintained between 0 and 5 °C. The resulting solution was stirred at 0 °C for 3 min before being cooled to −78 °C by a dry ice−acetone bath. A solution of ester 6 (5.00 g, 32.0 mmol) in THF (41.3 mL) was added dropwise to the LDA solution over 45 min while the inside temperature was maintained below −73 °C, and the resulting solution was stirred at −78 °C for 20 min to form an orange (or dark orange) solution of dianion. A separate flask was charged with *N*-fluorobenzenesulfonimide (14.1 g, 44.8 mmol) and THF (62 mL), and the resulting solution was cooled to −96 °C by a liquid nitrogen−acetone bath. The solution of the dianion was added via an addition funnel to the suspension of the fluorinating reagent over 1 h while the internal temperature was maintained around −95 °C. The funnel and the flask were flushed with 2.5 mL of THF into the reaction mixture. The resulting mixture was stirred at −96 °C for 1 h before being warmed to −20 °C over 30 min. Acetic acid (11 mL) in THF (5 mL) was added slowly over 7 min. The mixture was allowed to warm to ambient temperature after the addition of MTBE (100 mL). The resulting solid was removed by filtration and was washed thoroughly with MTBE (6 × 70 mL). The combined filtrate and wash were filtered again and analyzed by HPLC. The chemical yield was 86%. The filtrate was passed through a short plug of silica gel (20 g), and the plug was washed with MTBE (200 mL). The combined MTBE solutions were concentrated under reduced pressure. The

(18) Tsumoda, T.; Suzuki, M.; Nojori, R. *Tetrahedron Lett.* **1980**, *21*, 1297.

(19) Nakazato, A.; Kumagai, T.; Sakagami, K.; Tomisawa, K. worldwide patent number WO00/58358, 2000.

residue was dissolved in EtOAc (250 mL) and washed with saturated aqueous $NaHCO_3$ (170 mL). The aqueous layer was back-extracted with EtOAc (2 × 60 mL). The combined organic solutions were washed with brine (60 mL) and dried over Na_2SO_4. Evaporation of solvent gave 5.76 g of crude ester, which was subjected to bulb-to-bulb distillation (1.6 Torr) to afford 4.87 g of ester 7 as a yellow oil.

An analytically pure sample was obtained by further flash silica gel column chromatography to give 7 as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.54 (m, 1 H), 5.55 (m, 1 H), 4.95 (dd, J = 48.5, 5.5 Hz, 1 H), 4.49 (dt, J = 7.2, 4.6 Hz, 1 H), 3.82 (s, 3 H), 3.11 (dm, J = 24.4 Hz, 1 H), 2.75 (m, 1 H), 2.51 (s, 1 H), and 2.33 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0 (d, J = 24.1 Hz), 132.3, 126.1 (d, J = 5.0 Hz), 89.5 (d, J = 186.0 Hz), 73.9 (d, J = 4.0 Hz), 57.1 (d, J = 20.1 Hz), 52.6, and 41.8; ^{19}F NMR (377 MHz, $CDCl_3$) δ −196.5; IR (film) 3409, 3059, 1744, 1439, 1288, 1209, 1153, 1099, 1048, 951, 733 cm^{-1}; $[\alpha]_D^{25}$ −123.5 (c 1.02, $CHCl_3$). HRMS calcd for $C_8H_{11}FO_3$ (M + H^+) 175.0770, found 175.0773.

Methyl (2*S*)-Fluoro[(1*R*,2*S*,3*R*,5*S*)-3-hydroxy-6-oxabicyclo[3.1.0]hex-2-yl]acetate (8). To a solution of olefin 7 (1.92 kg, 11.0 mol) in toluene (4.63 L) was added vanadyl acetylacetonate ($VO(acac)_2$, 58.3 g, 0.22 mol) at 0 °C. After a solution of TBHP (5.7 M in decane, 38.6 mL) was added to the solution at 0 °C, the resulting suspension was allowed to warm to 14 °C. An additional solution of TBHP (5.7 M in decane, 4.36 L) was slowly added to the reaction mixture over 50 min while maintaining the batch temperature between 14 and 28 °C. The resulting suspension was stirred for another 2 h, and then heated at 40 °C for 8 h. Excess TBHP was quenched with aqueous $Na_2S_2O_3$ solution (2.95 kg of $Na_2S_2O_3$ and 4.71 kg of H_2O), which was slowly added at 0 °C. The resulting mixture was stirred at 20 °C for 1.5 h. The disappearance of peroxides was confirmed by test paper. The aqueous layer was separated and extracted with EtOAc (2 × 9.42 L). The combined organic solutions were washed with brine (5.33 L). The brine layer was back-extracted with EtOAc (4 × 3.42 L). GC assay of the combined organic solutions indicated 1.90 kg (91%) of product 8. The combined organic solutions were concentrated, and the resulting residue was purified by silica gel chromatography in a filter pot (first eluted with hexanes/EtOAc (4/1) then pure EtOAc).

Analytically pure sample was prepared by flash silica gel column chromatography (hexanes/MTBE) followed by recrystallization (EtOAc) to give 8 as a pale yellow solid: mp 31–33 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 5.01 (dd, J = 48.3, 3.9 Hz, 1 H), 4.13 (br s, 1 H), 3.86 (s, 3 H), 3.71 (m, 1 H), 3.59 (m, 1 H), 2.77 (dd, J = 39.5, 7.9 Hz, 1 H), 2.39 (br s, 1 H), and 2.30 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4 (d, J = 24.1 Hz), 88.1 (d, J = 186.1 Hz), 73.2 (d, J = 1.6 Hz), 58.4, 57.1 (d, J = 5.6 Hz), 52.8, 51.6 (d, J = 19.3 Hz), and 37.7 (d, J = 1.6 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ −200.8 (dd, J = 48.3, 39.5 Hz), LRMS m/z 191 (M + 1), 129 (M − 1), 172 (M − $H_2O]^+$), 59 ($(COOCH_3)^+$, base peak); $[\alpha]_D^{25}$ −56 (c 1.0, $CHCl_3$). Anal. Calcd for $C_8H_{11}FO_5$: C, 50.53; H, 5.83; F, 9.99. Found: C, 50.36; H, 5.92; F, 10.05.

Methyl (2*S*)-((1*R*,2*R*,3*R*,5*S*)-3-[(*tert*-Butyl(dimethyl)silyl]oxy]-6-oxabicyclo[3.1.0]hex-2-yl)(fluoro)acetate (9). To a solution of epoxy alcohol 8 (1.60 kg, 8.40 mol) and DMF (3.40 L) was added imidazole (1.26 kg, 18.5 mol) at 10 °C. TBSCl (1.52 kg, 10.1 mol) was added to the reaction mixture while maintaining the batch temperature below 8 °C. The resulting solution was stirred at 5 °C for 10 min, then allowed to warm to 20 °C over 30 min and stirred for 2 h at the same temperature. The consumption of the starting alcohol was monitored by GC, and the reaction mixture was diluted with cold toluene (17.0 L, 5 °C). The resulting mixture was washed with H_2O (5.67 L), saturated aqueous $NaHCO_3$ (5.67 L), H_2O (2 × 5.67 L), and brine (5.67 L). HPLC assay of the organic solution indicated 2.38 kg (92%) of 9. Concentration of the solution gave 9 as a yellow liquid, which was used for the next step without further purification.

An analytically pure sample was obtained by flash silica gel column chromatography (hexanes/MTBE) to give 9 as a colorless solid: mp 28–30 °C; ^1H NMR (490 MHz, $CDCl_3$) δ 5.00 (dd, J = 48.2, 3.5 Hz, 1 H), 4.45 (m, 1 H), 3.85 (s, 3 H), 3.51 (m, 1 H), 3.42 (m, 1 H), 2.64–2.52 (dm, J = 34.5 Hz, 1 H), 2.14 (m, 1 H), 1.91 (m, 1 H), 0.88 (s, 9 H), 0.084 (s, 3 H), and 0.051 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8 (d, J = 24.1 Hz), 88.3 (d, J = 186.1 Hz), 75.4 (d, J = 1.6 Hz), 58.3, 57.2 (d, J = 7.2 Hz), 52.8 (d, J = 19.3 Hz), 52.7, 38.3, 25.9, 18.0, −4.5, and −4.7; ^{19}F NMR (377 MHz, $CDCl_3$) δ −199.9 (dd, J = 48.2, 34.5 Hz); LRMS m/z 305 (M + 1), 121 (base peak); $[\alpha]_D^{25}$ −27 (c 1.0, $CHCl_3$). Anal. Calcd for $C_{14}H_{29}FO_5Si$: C, 55.23; H, 9.28; F, 6.24. Found: C, 55.27; H, 8.63; F, 6.31.

Methyl (1*R*,2*R*,4*S*,5*S*,6*R*)-2-[(*tert*-Butyl(dimethyl)silyl]oxy]-6-fluoro-4-hydroxybicyclo[3.1.0]hexane-6-carboxylate (10). To a solution of epoxide TBS-ether 9 (assay wt 1.50 kg, 5.24 mol) in THF (16.1 L) was added a solution of Et_3Al (1.0 M in hexanes, 6.81 L, 6.81 mol), while maintaining the batch temperature at −60 °C over 1 h, and the resulting solution was stirred at −60 °C for 20 min. A solution of LHMDS (1.0 M solution in hexanes, 7.86 L, 7.86 mol) was added to the reaction mixture over 1 h while maintaining the batch temperature below −60 °C, and the reaction was aged at −60 °C. The progress of the reaction was monitored by GC. After complete consumption of the epoxide (6 h), an aqueous solution of citric acid (3 M, 10.6 L) was added over 1 h while maintaining the batch temperature below −50 °C. After MTBE (12.4 L) was added, the resulting suspension was allowed to gradually warm to 15 °C with stirring. Two liquid phases were produced after addition of H_2O (4.93 L). The organic layer was separated and washed twice with saturated aqueous $NaHCO_3$ (11.1 L then 5.6 L). GC assay of the organic solution indicated 1.54 kg (96%) of 10. Concentration of the organic layer afforded crude alcohol as a yellow oil, which was used for the next reaction without further purification.

An analytically pure sample was obtained by flash silica gel column chromatography to give 10 as a colorless glass: ^1H NMR (400 MHz, $CDCl_3$) δ 4.47 (d, J = 4.4 Hz, 1 H), 4.34 (m, 1 H), 3.83 (s, 3 H), 2.44 (d, J = 6.6 Hz, 1 H), 2.37 (d, J = 11.2 Hz, 1 H), 2.25 (d, J = 6.8 Hz, 1 H), 2.07 (m, 1 H), 1.84 (m, 1 H), 0.91 (s, 9 H), 0.131 (s, 3 H), and 0.128 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2 (d, J = 26.5 Hz), 79.7 (d, J = 244.3 Hz), 74.1, 74.0, 52.9, 44.8 (d, J = 10.4 Hz), 37.9 (d, J = 12.0 Hz), 37.6 (d, J = 11.2 Hz), 25.8, 18.0, −4.8, and −4.9; ^{19}F NMR (377 MHz, $CDCl_3$) δ −217.1 (m); LRMS m/z 305 (M + 1), 304 (M), 303 (M − 1), 75 (base peak); $[\alpha]_D^{25}$ +8.6 (c 1.9, $CHCl_3$). Anal. Calcd for $C_{14}H_{29}FO_5Si$: C, 55.23; H, 8.28, F, 6.24. Found: C, 55.44; H, 8.46; F, 6.39.

Methyl (1*R*,2*R*,4*S*,6*S*)-2-[(*tert*-Butyl(dimethyl)silyl]oxy]-6-fluoro-4-oxobicyclo[3.1.0]hexane-6-carboxylate (16). To a solution of bicyclic mono-TBS-diol 10 (2.00 g, 6.57 mol) in acetonitrile (6.0 L) at −5 °C was added acetic acid (0.70 L) and water (2.5 L), followed by $RuCl_3$ hydrate (14.20 g). To the mixture was added aqueous sodium hypochlorite solution (~13%; 7.0 L) over 2 h, keeping the temperature around 0 °C. The resulting mixture was stirred at 0 °C for another 1 h until all bicyclic mono-TBS-diol 10 disappeared, monitoring by TLC and NMR. The excess aqueous sodium hypochlorite was decomposed by the addition of 2-propanol (0.70 L) and aging at 0 °C for 15 min. The two layers were separated, and the organic solution was used for the next reaction without further treatment.

An analytically pure sample was obtained by flash silica gel column chromatography (MTBE/hexane) to give 16 as a colorless crystalline solid: mp 70–71 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 4.66 (d, J = 5.4 Hz, 1 H), 3.86 (s, 3 H), 2.73 (m, 2 H), 2.54 (dt, J = 19.1, 5.7 Hz, 1 H), 2.32 (dd, J = 19.1, 3.8 Hz, 1 H), 0.91 (s, 9 H), 0.13 (s, 3 H), and 0.11 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.2, 167.1 (d, J = 26.1 Hz), 78.9 (d, J = 246.4 Hz), 67.6 (d, J = 2.8 Hz), 53.4, 47.5 (d, J = 3.9 Hz), 42.0 (d, J = 11.4 Hz), 39.6 (d, J = 13.3 Hz), 25.7, 18.0, −4.76, and

–4.78; ^{19}F NMR (377 MHz, $CDCl_3$) δ –210.7; $[\alpha]_D^{25}$ + 58.3 (*c* 0.50, CH_2OH). Anal. Calcd for $C_{18}H_{32}FO_5Si$: C, 55.60; H, 7.67, F, 6.28. Found: C, 55.60; H, 7.56; F, 6.33.

Methyl (*1R,2R,5S,6S*)-6-Fluoro-3-hydroxy-4-oxobicyclo-[3.1.0]hexane-6-carboxylate (17). The above organic layer, containing TBS-ketone 16 (6.33 mol), was warmed to 22 °C and 1 M HCl (1.37 L) was added. The mixture was stirred at 22–24 °C for 3.5 h until cleavage of the TBS group was complete. To the mixture was added saturated sodium bicarbonate solution (4.8 L). The mixture was stirred for 15 min and diluted with isopropyl acetate (20 L), and the organic layer was separated. The aqueous layer was back extracted with isopropyl acetate (6 L). The combined organic solutions were concentrated to dryness, and the compound was purified by silica gel chromatography in a filter pot (first eluted with 30% MTBE in hexane then MTBE alone) to give 1.28 kg (95% from 10) of 17 as off-white crystals.

An analytically pure sample was obtained by further flash silica gel column chromatography to give 17 as a colorless crystalline solid: mp 61–62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.92 (br *s*, 1 H), 3.85 (*s*, 3 H), 2.86 (dd, J = 6.2, 2.1 Hz, 1 H), 2.71 (d, J = 6.2 Hz, 1 H), 2.61 (dd, J = 19.4, 5.7 Hz, 1 H), 2.58 (br *s*, 1 H), and 2.30 (dd, J = 19.4, 3.7 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.9, 167.0 (d, J = 26.2 Hz), 79.0 (d, J = 246.6 Hz), 67.0 (d, J = 3.1 Hz), 53.5, 46.8 (d, J = 4.2 Hz), 41.6 (d, J = 11.8 Hz), and 39.4 (d, J = 13.1 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ –210.8; $[\alpha]_D^{25}$ + 77 (*c* 0.50, CH_2OH). Anal. Calcd for $C_8H_9FO_4$: C, 51.07; H, 4.82, F, 10.10. Found: C, 51.06; H, 4.83; F, 10.06.

Methyl (*1S,4R,4'S,5R,5'S,6S*)-6-Fluoro-4-hydroxy-4',5'-diphenylspiro[bicyclo[3.1.0]hexane-3,2'-[1,3]dioxolane]-6-carboxylate (18). To a solution of hydroxy ketone 17 (1.09 kg, 5.76 mol) and CH_2Cl_2 (7.7 L) was added a solution of (*S,S*)-bis-*O*-TMS-hydrobenzoin (assay 2.01 kg, 5.60 mol) and CH_2Cl_2 (2.56 L). The solution was cooled to –20 °C. TfOH (50.9 mL; 0.576 mol) was charged through an addition funnel over 4 min at –15 to ca. –20 °C. The solution was warmed to –10 °C and aged at –10 °C for 1.5 h. An additional solution of (*S,S*)-bis-*O*-TMS-hydrobenzoin (assay 107 g; 0.298 mol) in CH_2Cl_2 (128 g) was charged to the reaction mixture at –10 °C. The reaction was completed after 30 min age at –10 °C. The reaction was quenched by addition of pyridine (46.9 mL, 0.576 mol) at < –15 °C. The solution was warmed to –10 °C, washed with 5 wt % of a cold aqueous solution of $NaHCO_3$ (8.76 L), 1 M cold aqueous HCl (8.6 L), 5 wt % of a cold aqueous $NaHCO_3$ (3.75 L), and 10 wt % of a cold aqueous solution NaCl (5.0 L) in turn and dried over Na_2SO_4 (1.5 kg). The solvent was switched into acetonitrile and the solution was used for the next reaction without further purification. HPLC assay of the solution indicated 2.06 kg (93%) of ketal alcohol 18.

An analytically pure sample was obtained by flash silica gel column chromatography to give 18 as a colorless crystalline solid: mp 118–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.21 (m, 10 H), 4.89 (d, J = 8.3 Hz, 1 H), 4.83 (d, J = 8.3 Hz, 1 H), 4.51 (br *s*, 1 H), 3.83 (*s*, 3 H), 2.54–2.51 (m, 2 H), 2.43–2.37 (m, 2 H), and 2.18 (br *s*, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7 (d, J = 25.7 Hz), 135.5, 135.3, 128.7, 128.5, 128.4, 126.9, 126.3, 117.7, 86.2, 86.1, 77.8 (d, J = 247.1 Hz), 71.1, 53.0, 45.7 (d, J = 7.8 Hz), 37.5 (d, J = 12.1 Hz), and 36.7 (d, J = 11.9 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ –216.3; $[\alpha]_D^{25}$ + 37.5 (*c* 0.80, $CHCl_3$). Anal. Calcd for $C_{28}H_{27}FO_5$: C, 68.74; H, 5.51. Found: C, 68.72; H, 5.43.

Methyl (*1S,4'S,5R,5'S,6S*)-6-Fluoro-4-oxo-4',5'-diphenylspiro[bicyclo[3.1.0]hexane-3,2'-[1,3]dioxolane]-6-carboxylate (19). To a solution of ketal alcohol 18 (assay 2.04 kg, 5.31 mol) in acetonitrile (36.7 L) was added $RuCl_3$ hydrate (3.25 g) followed by water (2.0 L) and acetic acid (0.41 L) at 0 °C. Aqueous sodium hypochlorite solution (~13%, 5.37 L) was added to the reaction solution slowly over 19 min, while maintaining the reaction temperature below 4 °C. The solution was aged at 0–3.5 °C for 2 h. The reaction was quenched by addition of 2-propanol (2.2 L) at 3.5 °C. After 30 min of aging at the same temperature, aqueous cold $NaHCO_3$ (6 wt %, 10.7 L) was added to the mixture over 12 min between 0.4 and 3.3 °C. The resulting slurry was stirred for 30 min at 3 °C, and the product 19 was filtered. The wet cake was washed with cold water (2 × 2 L) and dried to give the first crop (1.40 kg) of the ketal ketone 19. The filtrate and washes were combined and the layers were separated. The organic layer was concentrated in vacuo. The resulting slurry was filtered. The cake was washed with water (2 × 0.48 L) and was recrystallized from acetonitrile (1.8 L) and water (1.08 L) to give the second crop (0.46 kg) of 19. A total of 1.86 kg (91.6%) of ketal ketone 19 was obtained.

An analytically pure sample was obtained by flash silica gel column chromatography to give 19 as a colorless crystalline solid: mp 58.5–59.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.34 (m, 6 H), 7.28–7.25 (m, 4 H), 4.97 (d, J = 8.4 Hz, 1 H), 4.88 (d, J = 8.4 Hz, 1 H), 3.93 (*s*, 3 H), 3.10 (dd, J = 6.4, 2.0 Hz, 1 H), 2.94 (d, J = 4.0 Hz, 2 H), and 2.87 (d, J = 6.4 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.5, 166.9 (d, J = 25.7 Hz), 136.1, 135.3, 129.0, 128.8, 128.72, 128.69, 126.6, 126.5, 110.8, 86.3, 85.8, 78.9 (d, J = 251.6 Hz), 53.6, 48.3 (d, J = 3.3 Hz), 42.2 (d, J = 13.2 Hz), and 41.7 (d, J = 12.0 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ –208.5; $[\alpha]_D^{25}$ –61.0 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{28}H_{25}FO_5$: C, 69.10; H, 5.01. Found: C, 69.08; H, 4.86.

(*1S,4'S,5R,5'S,6S*)-6-Amino-4-cyano-6-fluoro-4',5'-diphenylspiro[bicyclo[3.1.0]hexane-3,2'-[1,3]dioxolane]-6-carboxamide (20). To a solution of 7 M ammonia in methanol (7.4 L, 47.8 mol) and $Ti(OPr^i)_4$ (1.77 L, 5.93 mol) at 23 °C was added ketal ketone 19 (2.11 kg, 1.89 kg as pure 19, 4.94 mol) and the mixture was stirred for 4 h at 20–23 °C. The mixture was cooled to –12 °C, and TMSCN (505 g, 5.09 mol) was added. The mixture was warmed to –4.5 °C and stirred at that temperature for 16 h. The mixture was filtered, and the cyanate were washed with cold MeOH (7.0 L) and dried at 20–25 °C at reduced pressure to afford 1.84 kg of aminonitrile 20 as a colorless solid.

An analytically pure sample was prepared by silica gel column chromatography to give 20 as a colorless crystalline solid: mp 196.8–197.4 °C. ^{1}H NMR (400 MHz, $DMSO\text{-}d_6$) δ 8.04 (*s*, 1 H), 7.78 (*s*, 1 H), 7.38–7.26 (m, 10 H), 5.15 (d, J = 8.8 Hz, 1 H), 4.81 (d, J = 8.8 Hz, 1 H), 2.86, (*s*, 2 H), 2.78 (dd, J = 14.5, 3.2 Hz, 1 H), 2.63 (d, J = 6.8 Hz, 1 H), 2.46 (d, J = 6.8 Hz, 1 H), and 2.23 (dd, J = 14.5, 4.4 Hz, 1 H); ^{13}C NMR (101 MHz, $DMSO\text{-}d_6$) δ 168.7 (d, J = 23.2 Hz), 136.5, 135.9, 128.6, 128.5, 128.5, 127.1, 126.9, 123.4, 115.1, 84.7, 84.3, 81.1 (d, J = 255.4 Hz), 54.8, 48.3 (d, J = 7.2 Hz), 36.6 (d, J = 11.2 Hz), and 35.9 (d, J = 10.4 Hz). ^{19}F NMR (377 MHz, $DMSO\text{-}d_6$) δ –221.8; $[\alpha]_D^{25}$ + 59.4 (*c* 1.0, DMF). Anal. Calcd for $C_{28}H_{26}FN_3O_3$: C, 67.17; H, 5.12; N, 10.68. Found: C, 67.16; H, 5.06; N, 10.50.

(1*R,2S,5S,6S*)-2-Amino-6-fluoro-4-oxobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid (1). A mixture of aminonitrile 20 (1.63 kg crude, 1.55 kg pure basis), HOAc (3.25 L), H_2O (3.25 L), and concentrated HCl (6.50 L) was heated to 75 ± 2 °C for 4 h. ^{19}F NMR showed that the reaction was complete. The solution was cooled to 18 °C and extracted with CH_2Cl_2 (1 × 9 L and 2 × 5 L). The aqueous layer was concentrated to ~2 L at 10–25 Torr and 50 °C internal temperature. The resulting slurry was cooled to 0 °C and stirred for 1 h. The cooled slurry was filtered, and the cake containing the HCl salt of product 1 was maintained under vacuum filtration for 5–10 min to remove as much of the filtrate as possible. The cake of HCl salt was added to water (5.0 L) at 65 °C, and rinsed in with hot H_2O (300 mL). The solution was allowed to cool to 17 °C over 45 min. The pH was adjusted to 1.26 with 50% NaOH (230 mL). The slurry was cooled to 0 °C and stirred for 45 min. The slurry was filtered, and the cake was washed with H_2O (2 × 1 L) and dried under nitrogen to afford 872 g of off-white crystalline product 1 in 94% yield as monohydrate:[26] mp 174.5–175.5 °C. ^{1}H NMR (400 MHz, TFA-*d*) δ 3.67 (d, J = 8.8 Hz, 1 H), 3.46 (d, J = 8.8 Hz, 1 H), 3.45 (dd, J = 6.1, 2.6 Hz, 1

H), and 3.16 (dd, J = 6.1, 26 Hz, 1 H). $[\alpha]_D^{25}$ + 73.2 (c 0.14, 1 M HCl). Other characterization data and biological data all matched with that reported and with that of an authentic sample provided by Dr. Atsuro Nakazato of Taisho Pharmaceutical Co.; Ltd.

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Supporting Information Available: Procedures and characterization data for compounds 24A/24, 25A/25, 26A/26, 28, 29, 30, 31, (−)-32(+)-32, 33, and 34, single X-ray structure of ketal ketone 19 (Figure 6), and ^{13}C NMR of 7 and 31. This material is available free of charge via the Internet at http://pubs.acs.org.

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